

# **Ketamine-Assisted Psychotherapy (KPT) of Heroin Addiction: Immediate Effects and Six Months Follow-Up**

Evgeny M. Krupitsky, M.D., Ph.D.  
Andrey M. Burakov, M.D., Ph.D.  
Tatyana N. Romanov, Ph.D.  
Alexander Y. Grinenko, M.D., Ph.D.  
Rick J. Strassman, M.D.

In the 20th century, while billions of dollars have been spent to treat addictive diseases, the search for effective medication continues. The mainstay of such treatments includes therapy and counseling, AA and NA, different kinds of rehabilitation programs, drug maintenance programs, and pharmacotherapy. The efficacy of all these suggested methods of addiction treatment is not enough, however, and still there is a need for new effective medications. The use of hallucinogens in the treatment of addictions could be one promising approach (Halpern, 1996).

Many addiction studies in the 1950's and 1960's (Grinspoon and Bakalar, 1979), suggested that hallucinogen-assisted (psychedelic) psychotherapy might be an efficient treatment, but different methodologies made it difficult to generalize across studies.

In the 1970's Savage and McCabe (1973) showed that LSD-assisted psychotherapy had a positive effect on the outcome of treatment of heroin addicts: 25% of the subjects treated with LSD remained abstinent from opiates for one year as opposed to only 5% of the control group of conventional weekly group psychotherapy.

The authors encouraged further research with hallucinogens in the treatment of addictions, but by 1973, when their study was published, human research with

these substances had essentially come to an end in America because of controversy associated with their non-medical use (Halpern, 1996).

Later in the 1980's and 1990's both animal studies and anecdotal human reports suggested anti-craving properties of another hallucinogen--ibogaine ("Endabuse") (Lotsof, 1995; Mash, 1998). However, further human research with ibogaine is needed to demonstrate its antiaddictive properties as well as safety.

Ketamine is a drug for general anesthesia, but in subanesthetic doses it induces a profound psychedelic (hallucinogenic) experience (Bowdle et al., 1998). Ketamine has several advantages over other hallucinogens as an adjunct to psychotherapy in the treatment of addictions: it is safe, short-acting, and, most importantly, it is not a scheduled drug like other hallucinogens. Our previous studies showed that ketamine-assisted psychotherapy is an effective method for alcoholism treatment (Krupitsky and Grinenko, 1997).

Also, ketamine could have anti-craving properties because of its influence on the NMDA receptor, similar to other NMDA receptor ligands-acamprosate and ibogaine (Mash et al., 1998; Sass et al., 1996). All these factors led us to study the efficacy of ketamine-assisted psychotherapy for heroin dependence.

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St. Petersburg Scientific-Research Center of Addictions and Psychopharmacology affiliated with St. Petersburg State Pavlov Medical University and the Leningrad Regional Center of Addictions, Novo-Deviatkinno 19/1, Leningrad Region 188661, Russia. E-mail: kru@lond.spb.su.

## Experimental Design and Methods

### Design

Seventy detoxified heroin addicts were randomly assigned to one of two groups. The patients of the experimental group received psychotherapy in combination with a "psychedelic" dose of ketamine (2.0 mg/kg i.m.). The patients of the control group received the same psychotherapy combined with a very low, non-psychedelic (non-hallucinogenic), dose of ketamine (0.20 mg/kg i.m.). This low dose induces some pharmacological effects but without inducing a peak psychedelic experience (see Results section below). Both the psychotherapist and patient were blind to the dose of ketamine. All patients were treated alike and were given the same preparation. The KPT sessions, regardless of dosage, were given under similar circumstances.

All patients' psychological and clinical evaluation during the treatment and follow-up period were performed by a clinician evaluator other than the psychotherapist providing KPT. This rater was also blind to the dose of ketamine.

### Patients

Seventy heroin addicts were screened, evaluated, and randomized in the study. Patients were recruited from the in-patient department of Leningrad Regional Center of Addictions. This is a regional center for the treatment of alcoholism and drug dependence with a 300-bed hospital. After they completed acute detoxification, informed consent was obtained from all patients prior to acceptance into the study. All patients were accepted into the study as in-patients and discharged from the hospital after they completed this treatment.

Information about the patients from the experimental and control groups is in Table 1. There were 35 heroin addicts (27 male and 8 female) in the experimental group and 35 heroin addicts (28 male and 7 female) in the control group. There were no statistically significant differences between the experimental and control groups with respect to age, duration of heroin addiction, and duration of abstinence from heroin.

Patients who participated in the study were mostly young people (Table 1). In this respect it is important to note that heroin addiction has a higher prevalence among youth in Russia. The typical age of heroin addicts in Russia is between 17 and 26. The typical duration of addiction is about 3-4 years. Many heroin addicts die because of overdosage or get imprisoned within the first several years of using heroin.

### Psychotherapist

Psychotherapy was provided by a psychotherapist (psychiatrist) specially trained in KPT. Only one KPT session was carried out for each patient.

### Patient selection

The following exclusion and inclusion criteria were employed:

Inclusion criteria:

- ICD-10/DSM-IV criteria of current heroin dependence, present for at least one year
- Age between 18 and 30
- At least high school education
- Abstinence from heroin and other substances of abuse for at least two weeks
- Not currently on psychotropic medication
- At least one relative willing to assist in follow-up and provide outcome data

Table 1. Information about groups of patients. Data expressed as MEAN (SEM)

Ketamine Dose	Information about patients		
	Age	Duration of heroin addiction (months)	Duration of abstinence before KPT (days)
High	23.03 (0.75)	31.66 (4.08)	25.29 (2.51)
Low	21.63 (0.51)	37.37 (3.88)	24.54 (1.7)

- Stable address within St. Petersburg or nearest district of Leningrad Region
- Home telephone number at which the patient could be reached
- Not currently on probation
- Competency to give informed consent and otherwise participate

Exclusion criteria:

- ICD-10/DSM-IV criteria of organic mental disorder, schizophrenic disorder, paranoid disorder, major affective disorder, and seizure disorder
- ICD-10/DSM-IV criteria for alcoholism or polydrug dependency
- Advanced neurological, cardiovascular, renal, or hepatic diseases
- Pregnancy
- Family history of psychiatric disorders listed above
- Clinically significant cognitive impairment
- Active tuberculosis or current febrile illness
- AIDS-defining illness
- Significant laboratory abnormality such as severe anemia, unstable diabetes, or liver function tests >3X above normal
- Pending legal charges with potential impending incarceration
- Concurrent participation in another treatment study
- Concurrent treatment in another substance abuse program

Screening evaluation included:

- Formal psychiatric examination
- Standard medical examination, including blood chemistry panel (including hepatic functions), urine analysis, HIV-test, pregnancy test and EKG
- Review of previous medical and psychiatric records

### **Assessment Instruments**

In choosing the battery of assessment instruments, care was taken to include those instruments we had already successfully used in our previous studies of KPT for alcoholism (Krupitsky and Grinenko, 1997) to provide comparability with those studies. There was also an effort to provide a mix of instruments widely used in psychotherapy outcome research. In addition, due to the specific nature of ketamine psychotherapy, instruments were considered desirable that might indicate changes in the areas of personality, life values and purposes, spiritual development, and unconscious emotional attitudes.

Psychiatric symptoms and psychopathology were assessed with:

- ICD-10 Structured clinical interview for psychiatric disorders (PSCI).
- Zung self-rating depression scale (ZDS) (Zung, 1965) - to assess depression.
- Spielberger self-rating state-trait anxiety scale (SAS) (Spielberger et al., 1976) - to assess state and trait anxiety.
- Visual analog scale of craving (VASC) - 100 mm line marked by subjects relative to the intensity of craving experienced while completing the scale.
- Scale of Anhedonia syndrome (SA) (Krupitsky et al., 1998)--this scale was developed to assess the severity of the syndrome of anhedonia. Many detoxified heroin addicts report that the termination of withdrawal leads to a syndrome of anhedonia which includes affective symptoms (mostly depression), anxiety, tension, irritation, feeling like life is dull and empty, passivity, sleep disturbance, and craving for heroin. SA has affective, cognitive, and behavioral subscales.
- Hallucinogenic Rating Scale (HRS) (Strassman et al., 1994)-to assess acute subjective response to a psychoactive drug challenge.

Psychological assessments:

- Minnesota Multiphasic Personality Inventory (MMPI) (Dahlstrom et al., 1972)--to assess personality characteristics.
- Locus of Control Scale (LCS) developed by Rotter (Phares, 1976) and adapted in Russia by Bazhin et al. (1993) - to assess the ability of the patients to control and manage different situations in their lives.
- Color Test of Attitudes (CTA) (Etkind, 1980) - to assess nonverbal unconscious emotional attitudes. The methodology of CTA had been described in detail previously (Krupitsky and Grinenko, 1997).
- Questionnaire of Terminal Life Values (QTLV) developed by Senin (1991) and based on the Rokeach's approach to the human values and beliefs (Rokeach, 1973) - to assess patient's value system.
- Purpose-in-Life Test (PLT) (Crumbaugh, 1968) based on Frankl's (1978) concept of the individual's aspiration for meaning in life--to assess one's meaning of his or her life. PLT was adapted in Russia by Leontiev (1992).
- Spirituality Changes Scale (SCS) based on the

combination of the Spirituality Self-Assessment Scale developed by Whitfield (1984), who studied the importance of spirituality in Alcoholics Anonymous, and the Life Changes Inventory developed by Ring (1984) to estimate psychological changes produced by near-death experiences. SCS has been shown to be sensitive to the changes in spirituality in our studies of KPT in alcoholism. It has also been shown to be useful in studies of meditation's effect on spiritual development (Krupitsky and Grinenko, 1997).

- Self-feeling - Activity - Mood Scale (SFAM) - specially calibrated 24-item visual analog scale arranged for the patient to assess quantitatively different aspects of his/her self-feeling (physical health), activity in everyday life, and mood.

We used specially-adapted Russian versions of the international scales and questionnaires mentioned above.

#### **Treatment Assessment, Outcome, and Follow-Up**

Assessment schedule:

- PSCI was administered only pre-therapy (baseline).
- ZDS, SAS, VASC, SA, MMPI, LCS, CTA, QTLV, PLT, and SFAM were administered pre-therapy (baseline) and post-therapy (during the week after the ketamine session) as a comprehensive test battery sensitive to the changes over the course of this study.
- SCS and HRS were administered only post-therapy to assess corresponding spirituality changes and acute subjective effects of the drug treatment.
- ZDS, SAS, VASC, and SFAM also were administered at 1, 3, 6, 12, 18, and 24 months after treatment was completed, in those patients who were abstinent from heroin.

Also, all patients were asked to write a detailed self-report about their experiences during the ketamine session. These self-reports provided evidence for the presence of a peak experience during the ketamine session.

#### **Follow-Up Data**

Follow-up data were collected on a monthly basis for up to 24 months (if the patient had not relapsed before that) by psychiatrists who were blind to ketamine dose. Follow-up data included:

- Information from the patient about his/her drug use during the follow-up period.
- Examination for evidence of injection sites over

the patient's veins.

- Information from the patient's relatives and/or colleagues about his/her drug use.
- Urine drug testing at 1, 3, 6, 12, 18, and 24 months after completion of therapy.
- ZDS, SAS, VASC, and SFAM data at 1, 3, 6, 12, 18, and 24 months.

#### **Treatment Procedure**

Patients and the psychotherapist were both blind to the dose of ketamine. There were up to 10 hours of psychotherapy provided before the ketamine session in order to prepare patients for the session. There were up to 5 hours of psychotherapy provided after the ketamine session to help patients interpret and integrate their experiences during the session into everyday life.

An anesthesiologist was present throughout the ketamine session to respond to any complications. The length of the ketamine session was about 1.5 to 2 hours. Only one ketamine session was carried out for each patient. The patient was instructed to recline on a couch and put on eyeshades. Pre-selected stereophonic music was used throughout the ketamine session. The psychotherapist provided emotional support for the patient and carried out psychotherapy during the ketamine session. Psychotherapy was existentially-oriented, but also took into account the patient's individuality and personality problems (Krupitsky and Grinenko, 1997). One and the same psychotherapeutic technique (see below) was used regardless of the dose of ketamine. Patients were discharged from the hospital soon after the KPT.

#### **Description of the Psychotherapeutic Technique Provided**

Three main stages in our method of KPT can be distinguished (Krupitsky and Grinenko, 1997). The first stage is preparation. In this stage, preliminary psychotherapy is carried out with patients. During these psychotherapeutic sessions it is explained to the patients that the relief from their dependence on heroin will be induced in a special state of consciousness in which they will have deep experiences that will help them to realize the negative effects of heroin abuse, and the positive aspects of life without drugs. We explain that the ketamine session may induce important insights concerning their personal problems, their system of values, notions of self and the world around them, and the meaning of their lives.

All of these insights may entail positive changes in their personality, which will be important for their shift to a new lifestyle without heroin. During the ketamine sessions, patients often experience the sepa-

ration of consciousness from the body and the dissolving of the ego, so it is very important to prepare patients carefully for such an unusual experience. The therapist pays close attention to such issues as the patient's personal motives for treatment, his goals for his new life without drugs, his idea of the cause of his disease and its consequences, and so on.

An individually tailored "psychotherapeutic myth" is formed during this dialogue. It becomes the most important therapeutic factor responsible for the psychological content of the second stage of the KPT. It is also very important to create a specific atmosphere of confidence and mutual understanding between the psychotherapist and patient during this first stage of KPT.

The second stage is the ketamine session itself. With a background of special music (generally, "New Age" composers, such as Kitaro and Jean Michel Jarre) the patient having a KPT session is treated psychotherapeutically. The content of these psychotherapeutic influences is based on the concrete data of the patient's anamnesis (case history) and is directed toward the resolution of the patient's personality problems and toward the formation of a stable orientation towards life without drugs.

We try to help our patients create a new meaning and purpose in life during this session. We emphasize the positive values and meaning of life without drugs and the negative aspects of drug abuse during the ketamine session. It is also very important to carefully direct the patient's psychedelic experiences by verbal influences and manipulating the musical background towards the symbolic resolution of the personality conflicts as well as a final cathartic peak experience. This second stage of KPT is conducted by two physicians, a psychotherapist, and an anesthesiologist, because some complications and side-effects (such as increased

blood pressure and depression of breath) are possible, though exceedingly rare. After the session, the patient rests, and we ask them to write down a detailed self-report of their experience later that evening.

In the third stage, special psychotherapeutic sessions are carried out within several days after the KPT session. During these sessions the patients discuss and interpret the personal significance of the symbolic content of their experience with the psychotherapist.

This discussion is directed toward helping the patient establish a connection between their ketamine experience and their intra- and interpersonal problems (primarily those connected with drug abuse), and thereby to solidify their desire for a life without drugs. We try also to assist patients to integrate the insights from the ketamine session into everyday life. The uniquely profound and powerful ketamine experience often helps them to generate new insights that enable them to integrate new, often unexpected, meanings, values and attitudes about the self and the world.

#### Data Management and Statistical Analysis

All patient related information was filed under a study code number for purposes of confidentiality and to maintain the double-blind design.

Statistical analyses using ANOVA as well as Student's t-test for dependent and independent samples were performed to assess treatment effects, outcome within both experimental and control groups, and significance of differences between the experimental and control groups. The statistical package "Statistica" ("STATISTICA for Windows," release 5.0 A, StatSoft, Inc., OK) was used. Independent variables were treatment (high or low dose of ketamine), and time of assessment (before KPT, after KPT, or during the follow-up). Dependent variables were clinical and psychological ratings as well as rate of abstinence and relapse.

Table 2. Characteristic of ketamine experience. Data expressed as Mean (SEM).

Ketamine Dose	Subscales of Hallucinogenic Rating Scale (HRS)					
	Intensity	Somaesthesia	Affect	Perception	Cognition	Volition
High	1.84 (0.12)***	1.7 (0.10)***	2.22 (0.12)***	1.74 (0.15)**	2.31 (0.10)***	2.39 (0.20)
Low	1.11 (0.15)	0.98 (0.15)	1.43 (0.12)	0.86 (0.15)	1.28 (0.19)	2.05 (0.18)

Statistical significance of differences between the high dose and low dose group: \* p<0.05; \*\* p<0.01; \*\*\* p<0.001

Table 3. Six months follow-up data. Data expressed as Mean (SEM).

High dose ketamine group						
Follow-up	Number of subjects (% of subjects) (According to the months of follow-up)					
	1 <sup>st</sup> month	2 <sup>nd</sup> month	3 <sup>rd</sup> month	4 <sup>th</sup> month	5 <sup>th</sup> month	6 <sup>th</sup> month
Abstinence	30 (85.7)**	25 (71.4)**	19 (54.3)*	18 (51.4)*	15 (42.9)*	13 (37.2)*
Relapse	3 (8.6)***	8 (22.9)***	14 (40.0)*	15 (42.9)*	17 (48.6)**	19 (54.3)*
No follow-up information	2 (5.7)	2 (5.7)	2 (5.7)	2 (5.7)	2 (5.7)	2 (5.7)
Specific circumstances for abstinence	—	—	—	—	1 (2.8)	1 (2.8)

Low dose ketamine group						
Follow-up	Number of subjects (% of subjects) (According to the months of follow-up)					
	1 <sup>st</sup> month	2 <sup>nd</sup> month	3 <sup>rd</sup> month	4 <sup>th</sup> month	5 <sup>th</sup> month	6 <sup>th</sup> month
Abstinence	19 (54.3)	13 (37.2)	10 (28.6)	10 (28.6)	6 (17.1)	6 (17.1)
Relapse	15 (42.9)	21 (60.0)	23 (65.7)	23 (65.7)	27 (77.2)	27 (77.2)
No follow-up information	1 (2.8)	1 (2.8)	2 (5.7)	2 (5.7)	2 (5.7)	2 (5.7)
Specific circumstances for abstinence	—	—	—	—	—	—

\* See notes for Table 2

## Results and Discussion

### Characteristics of Ketamine Experience

Content and features of the ketamine experience in both groups were evaluated with the Hallucinogenic Rating Scale (Strassman et al., 1994) (Table 2). HRS scores in the high-dose group provided evidence that patients in the experimental group had a profound psychedelic (hallucinogenic) experience. The scores in the high-ketamine dose group are similar to ones induced by a high (psychedelic) dose of another hallucinogen-dimethyltryptamine (DMT) in Strassman's study in healthy volunteers (Strassman, 1996). Average scores in the experimental group are also similar to the scores

obtained by Bowdle and co-authors with a high level of ketamine in the blood (200 ng/ml) (Bowdle et al., 1998).

HRS scores in the low ketamine dose group suggest that patients did not have a full-blown psychedelic (hallucinogenic) experience. However, HRS scores in the low-dose group were much higher than those seen in placebo groups in Strassman's (1996) and Bowdle's (1998) studies. Subjects in the low dose group demonstrated affective and cognitive effects that were close to a psychedelic dose of DMT. Thus, patients in the control group had experiences of what might be referred to as "sub-psychedelic." This effect could be the result of set and setting combined with a relatively low dose of ketamine. Similar effects were noted in a

Kurland et al (1971) study many years ago. They used 500 mcg of LSD as their high dose, and 50 mcg for their low dose, in treating alcoholics. They anticipated that 50 mcg would be an active placebo, yet they found the frequency of peak experiences similar in both groups. This finding is also a strong statement about the importance of set and setting in determining the responses to hallucinogenic drugs.

It is also very important to note that differences between HRS scores in the experimental and control groups in our study were statistically significant for all HRS subscales except Volition (Table 2). That means that the experiences of the high-dose ketamine group were different from those in the low-dose group. Patients in the experimental group had a deep psychedelic experience whereas patients of the control group experienced something like ketamine-facilitated guided imagery (Leuner, 1977). Patients of the control group, however, were often very much impressed by their experiences and considered them as useful and therapeutic ones.

**Treatment Outcome: Six Months Follow-Up Data**

Follow-up data were collected by psychiatrists who were blind to the dose of ketamine used for KPT. The follow-up data included information from patients themselves, their relatives, and urine drug testing results. Six months follow-up data are presented in Table 3.

According to the follow-up data, all patients were divided into four groups: patients who were abstinent, patients who relapsed, patients for whom we were unable to get reliable follow-up data, and patients with specific circumstances for abstinence. One patient from the experimental group was placed into the group with specific circumstances for abstinence: he was imprisoned on the fifth month of the follow-up for a crime committed

before his admission into the treatment program.

The rate of abstinence in the experimental (high dose) group was approximately twice as high as that of the control (low dose) group, while the corresponding rate of relapse was lower (Table 3). The differences between the experimental and control group in rates of both abstinence and relapse were statistically significant within the first six months of follow-up. Thus, KPT with the high dose of ketamine was significantly more effective within the first six months after the ketamine session.

It is important to note that almost 50% of patients in the experimental group and 60% of subjects in the control group relapsed within the first three months after KPT. Thus, it might be possible that repeated sessions carried out within the first few months after KPT would provide a higher rate of abstinence. Halpern (1996) in his review of the studies of hallucinogen-assisted psychotherapy of addictions came to a similar conclusion. However, testing of that hypothesis is a subject for a separate study.

**KPT Influence on Craving for Heroin**

KPT sessions significantly reduced craving for heroin as evaluated by the Visual Analog Scale of Craving in both experimental and control groups (Table 4). However, the decrease of craving in the experimental group was significantly greater than in the control group right after KPT as well as at one and three months after the ketamine session. Also, craving in the experimental group was significantly decreased for each of the six months following KPT, whereas in the control group this was the case for only the first month.

Thus, KPT with a high dose of ketamine produced greater and longer-lasting decrements in drug craving in heroin addicts than that seen in the low-dose group.

Table 4. KPT influence on craving for heroin. Data expressed as Mean (SEM).

Scores of the Visual Analog Scale of Craving for Heroin (VASC)					
Ketamine Dose	Before KPT	After KPT	1 month	3 months	6 months
High	29.24 (4.69)	3.97 (0.86) <sup>+++***</sup>	7.72 (2.65) <sup>+++*</sup>	5.5 (3.70) <sup>++**</sup>	9.25 (4.53) <sup>+</sup>
Low	36.34 (4.20)	15.06 (2.80) <sup>+++</sup>	20.18 (4.78) <sup>+</sup>	28.33 (8.06)	19.75 (5.14)

Statistical significance of differences between the scores before KPT and later scores:  
 + p<0.05; ++ p<0.01; +++ p<0.001; for other differences see Table 2

Table 5. KPT influence on the syndrome of anhedonia. Data expressed as mean (SEM).

Scores of the Scale of Anhedonia (SA)						
Ketamine Dose	Affective subscale		Cognitive subscale		Behavioral subscale	
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT
High	10.08 (1.91)	4.58 (1.37) <sup>++</sup>	4.67 (0.86)	1.25 (0.49) <sup>+++</sup>	2.58 (0.57)	1.25 (0.33) <sup>+</sup>
Low	14.92 (2.14)	5.75 (1.63) <sup>++</sup>	5.17 (0.77)	2.25 (0.96) <sup>+</sup>	3.08 (0.40)	1.67 (0.57) <sup>++</sup>

For designations of statistically significant differences see Table 4

It is interesting to note that other NMDA receptor antagonists, such as ibogaine and acamprosate, appear to have a similar influence on craving (Sass et al., 1996; Mash et al., 1998).

**KPT Influence on the Syndrome of Anhedonia**

The Scale of Anhedonia Syndrome (Krupitsky et al., 1998) was used to evaluate the severity of the syndrome of anhedonia. KPT in both experimental and control groups significantly reduced the severity of all three components of the syndrome of anhedonia (Table 5). There were no significant differences between the experimental and control group in severity of the syndrome of anhedonia after KPT.

Decreases in the severity of anhedonia syndrome were slightly greater in the experimental group, however. The amelioration of the syndrome of anhedonia is an important aspect of relapse prevention (Krupitsky et al., 1998). Thus, the positive effect of KPT on the syndrome of anhedonia in heroin addicts might be important for relapse prevention and maintaining abstinence from heroin. KPT reduced the severity of the syndrome of anhedonia more quickly than did traditional treatment with selective serotonin reuptake in-

hibitors (SSRIs) which takes at least three weeks.

Also, KPT reduced the severity of all components of the anhedonia syndrome, including a cognitive one, while SSRIs influence mostly affective and behavioral components (Krupitsky et al., 1999).

**KPT Influence on Anxiety**

KPT in both experimental and control groups significantly reduced elevated pre-treatment levels of both state and trait anxiety, measured with the Spielberger Anxiety Scale (Table 6). The level of anxiety was within normal limits by six months of abstinence in both groups. There were no significant differences between the experimental and control groups in the level of anxiety. It is evident that a low level of anxiety is favorable for abstinence from heroin.

**KPT Influence on Depression**

KPT in both experimental and control groups significantly reduced elevated levels of pre-treatment depression, measured by the Zung Depression Scale (Table 7). The level of depression was relatively low within the first six months after KPT in both groups. There were no significant differences between the ex-

Table 6. KPT influence on anxiety. Data expressed as Mean (SEM).

Scores of State-Trait Anxiety Scale (SAS)										
Ketamine Dose	State Anxiety		Trait Anxiety		1 month		3 months		6 months	
	Before KPT	After KPT	Before KPT	After KPT	State Anxiety	Trait Anxiety	State Anxiety	Trait Anxiety	State Anxiety	Trait Anxiety
High	41.17 (1.95)	35.71 (1.46) <sup>++</sup>	45.97 (1.67)	42.23 (1.54) <sup>++</sup>	35.81 (1.90) <sup>+</sup>	39.54 (1.88) <sup>+</sup>	35.62 (2.00)	37.61 (1.70) <sup>++</sup>	38.00 (2.69)	37.33 (1.64) <sup>++</sup>
Low	45.11 (2.01)	38.06 (1.79) <sup>++</sup>	46.69 (1.48)	40.74 (1.41) <sup>+++</sup>	35.26 (1.75) <sup>++</sup>	40.13 (1.69) <sup>++</sup>	37.17 (2.16) <sup>+</sup>	37.58 (2.04) <sup>++</sup>	35.88 (2.77) <sup>+</sup>	36.5 (2.65) <sup>++</sup>

For designations of statistically significant differences see Table 4



Table 7. KPT influence on depression. Data expressed as Mean (SEM).

Scores of Zung Depression Scale (ZDS)					
Ketamine Dose	Before KPT	After KPT	1 month	3 months	6 months
High	46.20 (1.51)	42.66 (1.56) <sup>++</sup>	39.88 (2.00) <sup>+</sup>	38.15 (1.79) <sup>++</sup>	40.50 (2.71)
Low	49.31 (1.57)	41.71 (1.74) <sup>+++</sup>	40.87 (1.42) <sup>+++</sup>	38.0 (2.61) <sup>+++</sup>	37.5 (2.27) <sup>++</sup>

For designations of statistically significant differences see Table 4

perimental and control groups in the level of depression. It is evident that a low level of depression is favorable for abstinence from heroin.

**KPT Influence on Self-Feeling (Feeling of Physical Health), Activity, and Mood**

KPT in both groups positively affected self-feeling (feeling of physical health), activity in everyday life, and mood, measured by the specially calibrated visual analog scales (Table 8). Self-feeling, activity in everyday life, and mood were significantly improved in both groups immediately and one month following KPT. In the control group self-feeling, activity, and mood differed significantly from pre-treatment levels even at six months follow-up (Table 8). These changes might favor abstinence from heroin.

**KPT Influence on Personality**

KPT in the experimental group produced a decrease in scores for the following MMPI scales: depression, conversion hysteria, paranoia, schizophrenia, and the Taylor scale of anxiety (Table 9). The self-sufficiency score significantly increased after KPT.

On the whole, such favorable psychological dynamics suggest that patients became more sure of themselves, their possibilities and their futures, less anx-

ious, less depressed and neurotic, and more emotionally open after KPT. These changes are very similar to those noted in alcoholics after KPT (Krupitsky and Grinenko, 1997) and are favorable for abstinence.

KPT in the control group decreased scores of the following scales: hypochondriasis, depression, conversion hysteria, masculinity-femininity, paranoia, psychasthenia, schizophrenia, sensitivity-repression, and Taylor scale of anxiety. The self-sufficiency score significantly increased after KPT (Table 9). Positive MMPI changes in the control group were similar to those in the experimental group and included even more scales.

However, the scores for the lie scale significantly increased while those for the validity scale decreased in the control group (Table 9). This may mean that control group patients tried to present themselves in a more positive, more socially acceptable way while they were answering MMPI questions after KPT.

Thus, positive MMPI changes in the control group might reflect to some extent patients' desire to appear in a more positive light.

**KPT Influence on the Locus of Control**

The locus of control in heroin addicts, evaluated with the Locus of Control Scale, became significantly

Table 8. KPT influence on self-feeling, activity, and mood. Data expressed as Mean (SEM).

Subscales of the Self-feeling - Activity - Mood Scale (SFAMS)															
Ketamine Dose	Self-feeling (feeling of physical health)		Activity in everyday life		Mood		1 month			3 months			6 months		
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	S	A	M	S	A	M	S	A	M
High	52.49 (1.67)	55.97 (1.43) <sup>*</sup>	53.71 (1.98)	58 (1.51) <sup>++</sup>	52.63 (1.84)	57.14 (1.58) <sup>+</sup>	57.79 (1.57) <sup>+</sup>	59.83 (1.76) <sup>+</sup>	59.25 (1.70) <sup>+</sup>	56.00 (2.56)	57.79 (2.93)	57.58 (2.31)	56.58 (2.47)	59.00 (2.37)	58.25 (2.26)
Low	49.11 (1.61)	56.11 (0.92) <sup>+++</sup>	50.49 (1.67)	58.23 (1.38) <sup>+++</sup>	48.94 (1.55)	57.34 (1.12) <sup>+++</sup>	55.09 (1.32) <sup>*</sup>	56.61 (1.49) <sup>+</sup>	56.26 (1.65) <sup>++</sup>	54.33 (2.60)	55.08 (3.14)	56.67 (2.68) <sup>*</sup>	57 (2.11) <sup>+</sup>	59.25 (2.57) <sup>*</sup>	59.38 (2.21) <sup>++</sup>

For designations of statistically significant differences see Table 4. S - self-feeling; A - activity; M - Mood

Table 9. KPT influence on the Scales of the Minnesota Multiphasic Personality Inventory (MMPI). Data expressed as Mean (SEM).

Ketamine Dose	Lie (L)		Validity (F)		Correction (K)		Hypochondriasis (Hs)		Depression (D)		Conversion hysteria (Hy)	
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT
High	44.13 (1.07)	47.08 (1.75)	73.33 (2.28)	69.92 (2.22)	47.83 (1.47)	51.17 (1.38)	54.96 (2.10)	51.46 (2.02)	62.21 (2.53)	53.79 (2.13) <sup>+</sup>	54.50 (1.86)	50.54 (1.65) <sup>+</sup>
Low	41.64 (0.71)	43.68 (0.98) <sup>+</sup>	76.27 (1.96)	71.59 (1.95) <sup>+</sup>	46.14 (1.71)	48.55 (1.79)	58.36 (2.15)	52.41 (2.09) <sup>++</sup>	67.14 (3.05)	59.27 (3.24) <sup>++</sup>	56.55 (2.05)	51.27 (2.20) <sup>++</sup>

  

Ketamine Dose	Psychopathic deviate (Pd)		Masculinity-femininity (Mf)		Paranoia (Pa)		Psychastenia (Pt)		Schizophrenia (Sc)		Hypomania (Ma)	
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT
High	74.83 (1.97)	72.92 (1.68)	60.88 (1.34)	58.88 (2.02)	65.42 (2.46)	60.92 (2.58) <sup>+</sup>	67.29 (2.15)	64.46 (2.16)	70.75 (2.11)	66.08 (2.83) <sup>+</sup>	74.38 (2.53)	74.08 (2.89)
Low	74.68 (2.15)	74.95 (2.26)	58.36 (2.10)	54.14 (1.70) <sup>+</sup>	69.14 (2.95)	64.86 (2.23) <sup>+</sup>	67.68 (2.73)	62.82 (2.31) <sup>+</sup>	77.00 (3.24)	67.55 (2.80) <sup>+++</sup>	73.50 (2.53)	71.23 (2.29)

  

Ketamine Dose	Social introversion (Si)		Iowa manifest anxiety (Taylor) (At)		Sensitivity-Represion (S-R)		Ego strength (Es)		Self-sufficiency (Sf)	
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT
High	50.08 (1.46)	49.58 (1.41)	23.21 (1.63)	19.04 (1.60) <sup>++</sup>	53.33 (3.40)	48.63 (2.69)	44.63 (2.55)	42.04 (2.45)	16.92 (0.88)	21.25 (1.85) <sup>+</sup>
Low	55.68 (1.54)	53.27 (1.66)	26.14 (1.95)	20.32 (1.74) <sup>+++</sup>	52.68 (4.62)	46.64 (3.62) <sup>+</sup>	49.55 (4.06)	46.64 (3.43)	18.64 (2.33)	20.82 (2.06) <sup>+</sup>

For designations of statistically significant differences see Table 4

more "internal" after KPT in both groups (Table 10). This result means that patients of both groups became more sure about their ability to control and manage different situations in their lives. They became more responsible for their lives and futures after KPT. In addition, locus of control in the case of failures became significantly more internal in the experimental group after KPT. This means that after KPT, patients of the experimental group assumed responsibility for

failures and problems in their lives. These positive changes might be favorable for abstinence from heroin.

**KPT Influence on Terminal Life Values**

KPT's influence on terminal life values was assessed with the Questionnaire of Terminal Life Values (QTLV) developed by Senin (1991), based on Rokeach's approach to human values and beliefs (Rokeach, 1973). KPT in the experimental group

Table 10. KPT influence on the locus of control in personality. Data expressed as Mean (SEM).

Subscales of the Locus of Control Scale (LCS)								
Ketamine Dose	Locus of control (total)		Locus of control in the area of achievements		Locus of control in the area of failures		Locus of control in the area of family life	
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT
High	4.12 (0.25)	5.18 (0.37) <sup>++</sup>	5.79 (0.32)	6.06 (0.34)	4.21 (0.34)	5.18 (0.31) <sup>+</sup>	4.68 (0.31)	5.06 (0.30)
Low	3.80 (0.21)	4.49 (0.23) <sup>++</sup>	5.14 (0.23)	5.49 (0.26)	4.29 (0.25)	4.66 (0.25)	4.54 (0.26)	4.74 (.23)

  

Ketamine Dose	Locus of control in the area of professional relationships		Locus of control in the area of interpersonal relationships		Locus of control in the area of health and disease	
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT
High	3.88 (0.21)	4.38 (0.32)	5.91 (0.36)	6.35 (0.29)	5.91 (0.30)	6.44 (0.29)
Low	4.40 (0.29)	4.46 (0.28)	5.71 (0.27)	5.74 (0.30)	5.77 (0.30)	5.71 (0.35)

For designations of statistically significant differences see Table 4

Table 11. KPT influence on the Questionnaire of Terminal Life Values (QTLV). Data expressed as Mean (SEM).

		Terminal life values									
Ketamine Dose	Social recognition		High standard of living		Creativity		Active social contacts		Self-perfection		
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	
High	29.71 (1.10)	33.4 (0.80) <sup>+++</sup>	35.34 (1.56)	34.49 (1.08)	28.51 (1.18)	31.03 (0.93) <sup>+</sup>	29.89 (1.07)	32.54 (0.91) <sup>+</sup>	32.94 (1.32)	35.09 (1.11)	
Low	29.76 (0.99)	32.62 (1.13) <sup>++</sup>	34.91 (1.19)	34.56 (0.95)	25.21 (1.07)	28.97 (0.84) <sup>+++</sup>	29.44 (0.98)	31.15 (0.93)	30.59 (1.06)	34.21 (0.82) <sup>+++</sup>	
		Terminal life values					Areas of life values' actualization				
Ketamine Dose	Achievement of life purposes		Spiritual contentment		Individual independence		Professional		Educational		
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	
High	33.77 (1.22)	35.40 (1.07)	34.51 (1.30)	36.49 (1.01)	30.51 (1.05)	33.8 (0.89) <sup>++++</sup>	53.37 (1.57)	56.43 (1.31) <sup>+</sup>	50.66 (2.21)	56.54 (1.68) <sup>+++</sup>	
Low	31.71 (1.04)	34.0 (0.81) <sup>+</sup>	31.62 (1.09)	34.12 (0.88) <sup>+</sup>	28.56 (1.07)	31.15 (0.84) <sup>++</sup>	50.18 (1.43)	54.15 (1.20) <sup>++</sup>	47.76 (1.72)	51.74 (1.62) <sup>+</sup>	
		Areas of life values' actualization									
Ketamine Dose	Family		Social life		Hobbies						
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT					
High	51.97 (1.44)	53.46 (1.46)	47.66 (1.83)	51.14 (1.48) <sup>+</sup>	52.54 (1.73)	53.49 (1.54)					
Low	50.35 (1.69)	53.65 (1.46) <sup>++</sup>	43.91 (1.53)	49.06 (1.55) <sup>+++</sup>	48.38 (1.68)	52.56 (1.36) <sup>++</sup>					

For designations of statistically significant differences see Table 4

caused a significant increase in the importance of values such as social recognition, creativity, social contacts, and individual independence. These factors were particularly relevant to areas of life values such as actualization as professional, educational, and social life (Table 11).

KPT in the control group brought about significant increases in the importance of social recognition, creativity, self-perfection, achievement of life purposes, spiritual contentment, and individual independence. These changes were significant in all five areas of life values actualization (Table 11). KPT-induced changes in the control group included even more QTLV scales than in the experimental group. However, the scores for individual independence and educational area of life values actualization were significantly greater after high dose, compared to low dose, KPT (Table 11).

Thus, KPT in both groups induced positive changes in terminal life values of heroin addicts. All these changes demonstrate an increased importance of life values other than the heroin "high" and thus might be favorable for abstinence from heroin.

### KPT Influence on Understanding the Meaning and Purpose of One's Own Life

KPT influence on understanding the meaning of one's own life was assessed using the Purpose-in-Life Test (PLT) based on Frankl's (1978) concept of the individual's aspiration for meaning in life. The PLT was adapted in Russian by Leontiev (1992). KPT caused a significant increase in the indices measuring understanding the meanings and purposes in life, as well as self-actualization, and the ability to control oneself and one's own life in accordance with those life purposes (Table 12). PLT changes after KPT were similar in both groups.

This result means that after KPT (regardless of the ketamine dose) patients were better able to understand the meaning of their lives, their life purposes, and gain perspective. After KPT, their lives became more interesting, emotionally deeper, and filled with meaning. They felt themselves better able to live in accordance with their concept of the meaning of life and life purposes as a result of KPT. Such changes might favor abstinence from heroin, particularly from the standpoint of Frankl's approach, which considers alcoholism and

Table 12. KPT influence on the purposes in life. Data expressed as the Mean (SEM).

Scales of the Purpose-in-Life Test (PLT)						
Ketamine Dose	Index of the understanding of the meaning of life		Understanding of Purposes in life		Meaning of the process of life	
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT
High	75.43 (3.55)	99.63 (3.44)***	22.26 (1.45)	30.11 (1.29)***	22.46 (1.19)	30.11 (1.06)***
Low	77.53 (3.49)	95.94 (3.42)***	23.65 (1.21)	28.47 (1.20)***	22.79 (1.07)	29.15 (1.02)***

  

Ketamine Dose	Self-actualization		Locus of control of self		Locus of control of life	
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT
High	16.80 (1.16)	22.94 (1.14)***	16.26 (0.95)	21.46 (0.82)***	20.20 (1.02)	25.26 (0.94)***
Low	19.09 (1.16)	21.76 (1.12)**	16.32 (0.88)	21.32 (0.78)***	21.26 (1.21)	25.18 (1.82)***

For designations of statistically significant differences see Table 4

addictions as an "existential neurosis," consequent to losing the meaning of life as well as the appearance of an "existential void" (Frankl, 1978). We believe KPT is able to fill this void, at least to some extent.

**KPT Influence on Spirituality**

A psychedelic ketamine experience is to some extent similar to the near-death experience (Jansen, 1997); it might be transformative and induce changes in spiritual development and even in worldview (Krupitsky and Grinenko, 1997). KPT effects on the spiritual development of heroin addicts were studied with the Spirituality Changes Scale (SCS). This instrument previously demonstrated a positive influence on spirituality by KPT in alcoholics. It also demonstrated beneficial effects of meditation in healthy volunteers (Krupitsky and Grinenko, 1997). In the current KPT study, the Spirituality Changes Scale demonstrated a similar increase in

the level of spiritual development after KPT in both groups of heroin addicts (Table 13). The SCS changes in heroin addicts were also similar to those induced by KPT in alcoholics in our previous studies (Krupitsky and Grinenko, 1997).

Many reports suggest that religious or spiritual conversion is an important factor in "spontaneous" recovery from drug abuse. Indeed, Twelve Steps and Alcoholics Anonymous programs have a distinctly spiritual/religious orientation (Corrington, 1989; Whitfield, 1984). A therapy that enhances the likelihood of a conversion experience therefore might have utility in the treatment of substance abuse. Ketamine-assisted psychotherapy may represent one method of eliciting spiritual experiences in patients with chemical dependence. The increased spiritual development induced by KPT in heroin addicts may be favorable for abstinence.

Table 13. KPT influence on spirituality. Data expressed as Mean (SEM)

Scores of Spirituality Changes Scale (SCS): The number of answers testifying to:					
Ketamine Dose	Significant increasing of spirituality	Moderate increasing of spirituality	Absence of changes	Moderate decreasing of spirituality	Significant decreasing of spirituality
High	11.41 (1.57)	15.79 (0.92)	10.09 (1.29)	1.53 (0.25)	1.50 (0.32)
Low	7.35 (1.71)	17.61 (1.35)	13.90 (1.62)	1.81 (0.26)	1.00 (0.30)

Table 14. KPT influence on non-verbal emotional attitudes. Data expressed as Mean (SEM).

Attitude to the images of the Color Test of Attitudes (CTA)										
Ketamine Dose	Me Now		The ideal image of self		Me in the past		Me in the future		My family	
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT
High	16.11 (1.14)	10.51 (0.94) <sup>+++</sup>	15.43 (1.19)	11.43 (1.18) <sup>++</sup>	24.97 (0.92)	26.63 (0.81)	15.43 (0.88)	12.4 (1.07) <sup>++</sup>	16.51 (1.29)	11.94 (1.26) <sup>++</sup>
Low	14.00 (1.36)	8.0 (0.91) <sup>++</sup>	11.09 (1.09)	9.66 (1.30)	24.23 (1.33)	26.60 (1.16)	14.69 (1.39)	11.66 (1.38)	14.69 (1.50)	10.91 (1.36) <sup>+</sup>

Ketamine Dose	My job		Heroin addict		A man abstaining from drugs		Psychiatrist	
	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT	Before KPT	After KPT
High	16.66 (1.24)	2.6 (1.08) <sup>+++</sup>	24.00 (1.18)	25.03 (1.19)	14.23 (1.16)	11.66 (1.13) <sup>+</sup>	14.86 (1.35)	12.17 (1.26) <sup>+</sup>
Low	16.46 (1.41)	11.77 (1.25) <sup>++</sup>	24.46 (1.55)	26.46 (1.38)	11.74 (1.33)	9.49 (1.21)	13.31 (1.49)	10.03 (1.31) <sup>+</sup>

For designations of statistically significant differences see Table 4. The lower the score, the more positive is the attitude to the image.

### KPT Influence on Non-Verbal Emotional Attitudes

KPT influence on nonverbal (mostly unconscious) emotional attitudes of heroin addicts was studied using the Color Test of Attitudes (CTA) (Etkind, 1980), which was valuable in evaluating the effects of KPT on non-verbal emotional attitudes of alcoholics (Krupitsky and Grinenko, 1997). According to the CTA data (Table 14), significant positive changes in the experimental group occurred in patient's nonverbal/unconscious assessments of their attitudes to the images "Me now," "The ideal image of self," "Me in the future," "My family," "My job," "A man abstaining from drugs," and "Psychiatrist" (that is, to 7 images out of 9). This finding means that the patients emotionally accepted these images and, in turn, incorporated attitudes towards abstinence connected with them. Thus, KPT may aid the treatment of heroin dependence by transforming unconscious attitudes related to abstinence. The enhancement of the positive relationship with the psychiatrist might also have had a therapeutic effect.

KPT-induced positive CTA changes in the control group were lower than in the experimental group and involved only four images: "Me now," "My family," "My job," and "Psychiatrist" (Table 14). Thus, high-dose KPT in heroin addicts produced greater changes in nonverbal unconscious emotional attitudes of heroin addicts than did low-dose KPT.

### Conclusion

The results of this double-blind randomized clinical trial of KPT for heroin addiction showed that high-dose (2.0 mg/kg) ketamine psychedelic psychotherapy

(KPT) elicits a profound, full psychedelic experience in heroin addicts.

On the other hand, low-dose KPT (0.20 mg/kg) elicits "sub-psychedelic" experiences that are very similar to ketamine-facilitated guided imagery. High-dose KPT produced a significantly greater rate of abstinence in heroin addicts within the first six months of follow-up than did low-dose KPT. High-dose KPT brought about a greater and longer-lasting reduction in craving for heroin, as well as greater positive change in nonverbal unconscious emotional attitudes.

Thus, it is possible that the higher rate of abstinence in the high-dose group was to some extent due to positive effects of ketamine on craving (which has been reported with other NMDA receptor ligands). It also may be due to the positive transformation of non-verbal unconscious emotional attitudes.

KPT-induced changes in depression, anxiety, anhedonia, and psychological changes on the verbal (conscious) level assessed with verbal tests (MMPI, Locus of Control Scale, Questionnaire of Terminal Life Values, Purposes-in-Life Test, and Spirituality Scale) were similar in the experimental and control groups. These results support the hypothesis that dramatic psychological transformations induced by psychedelic psychotherapy on the verbal level do not always lead to high rates of abstinence from drugs and alcohol (Grinspoon and Bakalar, 1979).

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